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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,715	MORI ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,9,10,12,13 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 9, 10, 12, 13, and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2, 6-8, 11, and 14 are cancelled
Claims 1, 3-5, 9, 10, 12, 13, and 15-22 are pending

This Office Action is in reply to Applicants' correspondence of 08/17/2006. Claims 2, 6-8, 11, and 14 are cancelled; no claims are withdrawn; claims 21 and 22 have been newly added; claims 1, 3-5, 9, 10, 12, 13, and 15-20 have been amended. Applicants' remarks and amendments have been fully considered but are not found to be persuasive. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn. This Action is made FINAL.

Claim Rejections - 35 USC § 103

1. In the rejection of claims under 35 USC 103, the required limitations of the claimed methods are noted. The base claim (i.e. claim 1) has been amended to include the limitation that the method comprises a step of 'selecting a rate of surface saponification and pore size of a solid phase, said solid phase being a porous film of a surface-saponified acetylcellulose'. Thus the claim requires only the step selecting a rate of saponification and a pore size, which is inherent in any use of saponified acetylcellulose, as acetylcellulose is inherently porous and any saponification would result in a saponification rate. The limitations are different than the previously presented claim 8, which required that a nucleic acid is separated and purified **by** selecting a surface saponification rate of acetylcellulose and a pore size of the porous film' (emphasis added). The current claims do not require, for example, selecting a length of a nucleic acid to be purified from a nucleic acid sample solution containing nucleic acids of different lengths, and selecting a rate of surface saponification and pore size of an acetylcellulose film such that the saponification rate and pore size are suitable separation and purification of the said nucleic acid to be purified.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 3-5, 10, 12, 15-18, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0512767 in view of US Patent 4,118,336, and US Patent 6,056,877.

With regard to claim 1, EP 0512767 teaches a method comprising the steps of adsorbing a nucleic acid onto a solid phase composed of an organic macromolecule having a hydroxyl group on the surface thereof, and desorbing the nucleic acid from the solid phase (p. 3, lines 19-30 and Example 6, p. 9). Regarding the other limitations of claim 1, the reference teaches the nucleic acid is in a sample solution (p. 4, lines 7-10), and also teaches washing the solid phase with a nucleic acid washing buffer after adsorbing and then desorbing the nucleic acid from the solid phase with a solution capable of desorbing the nucleic acid from the solid phase. Specifically, EP 0512767 teaches a step referred to as the "wash step" and suggest wash buffers (p. 3, lines 24-25), and teaches that the nucleic acid is desorbed using an elution buffer (p. 3, lines 27-28).

With regard to claim 12, EP 0512767 teaches a steps of treating a sample containing a cell or a virus with a nucleic acid solubilizing reagent (i.e. a lysis buffer) and then preparing the sample solution by adding an aqueous organic solvent to the solution. Specifically, EP 0512767 teaches that DNA is obtained in such a way that the procedure ends with a suspension of DNA in a solution such as a lysate, a step which inherently includes treating the sample with a solubilizing reagent (p. 3, lines 3-13). EP 0512767 teaches the subsequent addition of an organic solvent to the solution (p. 3, lines 19-22).

With regard to claim 15, EP 0512767 teaches the nucleic acid washing buffer that contains 50% ethanol, for example (p. 3, line 24).

With regard to claim 16, the desorbing solution has a salt concentration of 0.5 M or less (p. 3, lines 27-28).

With regard to claims 17 and 18, EP 0512767 teaches the use of a unit for isolation and purification that has a container with two openings that contains the solid phase and is attached to a differential pressure generator. Specifically, EP 0512767 teaches the use of a blotter which 'pulls liquid through a membrane' (p. 9, lines 5-15).

EP 0512767 does not teach a method wherein the macromolecule is surface-saponified acetylcellulose acetate or surface-saponified triacetlycellulose.

With regard to claims 1 and 3, the '336 patent teaches surface saponified cellulose diacetate and triacetate particles and suggest using these for purification of nucleic acids (Col. 9, lines 6-7; Col. 9, line 16; Col. 10, line 7). Additionally, the cellulose layer on the particles is inherently a porous film, and the reference teaches that the acetylcellulose has a saponification rate (Col. 9, lines 35-36)

With regard to claims 4 and 5, the '336 patent teaches surface saponified cellulose acetate particles wherein the saponification rate is 10% or more. For example, turning to example 1, the acetylation degree before saponification was 54.1% but less than 0.4% after saponification (Col. 9, lines 35-36).

With regard to claim 10, the cellulose acetate is coated on microcapsules, which are beads.

In addition, with regard to claim 17 the '336 patent exemplifies the use of the particles packed into a column, a structure that inherently has two openings.

Niether EP 0512767 nor the '336 patent teach the purification of a nucleic acid of predetermined length. The '877 patent teaches media and methods for polynucleotide separations. The reference teaches that polynucleotides of different predetermined lengths can be separated from a nucleic acid mixture by adsorbing and desorbing (referred to in the '877 patent as applying and eluting) a mixture of nucleic acids to a solid phase separation media (col.3 lns.9-16; Example 8). The reference indicates that separation particles and polymers may consist of a number of different substances, and specifically mentions the use of cellulose (col.3, lns.40-55). Relevant to claim 21, the '877 patent specifically teaches separation of nucleic acids of 10kb or less (e.g. col.30, Example 12).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the surface saponified cellulose triacetate taught by the '336 patent and the nucleic acid purification methods taught by EP 0512767 with the polynucleotide separation methods taught by the '877 patent. One would have been motivated to use the particles taught by the '336 patent in the separation methods taught by EP 0512767 in view of the teachings EP 0512767 that binding matrixes suitable for use in their invention include any hydrophilic surface (specifically mentioning particles as an option (p. 3, lines 49-52)). The '336 patent provides such a surface, and specifically suggest the use of the surface for the extraction and purification of nucleic acids (Col. 9, lines 6-7). It would have been further

obvious to use these methods and reagents for the separation of nucleic acids by size as exemplified by the methods of the '877 patent, which asserts that methods of chromatographic separation of nucleic acids are important because of their amenability to automation (col.1, ln.41), and specifically mentions the use of cellulose as a separation polymer. Therefore, in view of the teachings of EP 0512767 , the '336 patent, and the '877 patent, the claimed invention is *prima facie* obvious.

Response to Remarks

4. Applicants have traversed the rejection, arguing that the combined references fail to teach or suggest the elements of 'selecting a rate of surface saponification and pore size of a solid phase, said solid phase being a porous film of a surface-saponified acetylcellulose'. This argument and the amendments to the claims have been fully and carefully considered but are not found to be persuasive. As noted previously (see ¶ #1 above), the claims only require selecting a rate of surface saponification and a pore size, and have no requirement that the saponification rate and pore size are selected with specific regard to the 'nucleic acid having a predetermined length' that is separated and purified. As noted in the rejection, the '336 reference does teach the step of saponification of cellulose acetate, and the cellulose acetate is inherently porous (see also '336 reference col.8 lns.55-68). Thus in any method where cellulose aceteate is used, the user is inherently selecting a rate of saponification as well as a pore size.

The rejection is MAINTAINED.

5. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0512767 in view of US Patent 4,118,336, and US Patent 6,056,877 as applied to claims 1, 3-5, 10, 12, and 15-18 above, and in further view of US Patent 5,695,946.

The teachings of EP 0512767 in view of the '336 patent and the '877 patent are applied as they are applied in the rejection of claims 1, 3-5, 10, 12, and 15-18 previously in this office action.

EP 0512767 teaches using "typical" procedures for obtaining DNA from samples (p. 3, lines 5-6). EP 0512767 in view the '336 patent and the '877 patent does not teach a step wherein the nucleic acid solubilizing reagent comprises a guanidine salt, a surfactant, and a proteolytic enzyme.

The '946 patent teaches that target nucleic acid molecules are released from cells by treatment with any number of reagents, including guanidine salts, proteinase K and detergents (Col. 8, lines 7-12). The '946 patent exemplifies the use of the surfactant SDS for cell lysis (Col. 12, line 15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught EP 0512767 in view the '336 patent and the '877 patent, so as to have utilized a lysis buffer that included reagents that are typically considered lysis agents for the release of nucleic acids from sample cells. One would have been motivated by the teachings of EP 0512767 that any such typical methodologies for obtaining lysis solutions could be used and by the teachings of the '946 patent that each of these reagents are commonly used for the lysis of cells.

Response to Remarks

6. Applicants have traversed the rejection, arguing that the combined references fail to teach or suggest the elements of 'selecting a rate of surface saponification and pore size of a solid phase, said solid phase being a porous film of a surface-saponified acetylcellulose'. This argument and the amendments to the claims have been fully and carefully considered but are not found to be persuasive. As noted above, the cited references teach the required limitations as recited in the claims. The claims only require selecting a rate of surface saponification and a pore size, and have no requirement that the saponification rate and pore size are selected with specific regard to the 'nucleic acid having a predetermined length' that is separated and purified. As noted in the rejection, the '336 reference does teach the step of saponification of cellulose acetate, and the cellulose acetate is inherently porous (see also '336 reference col.8 lns.55-68). Thus in any method where cellulose acetate is used, the user is inherently selecting a rate of saponification as well as a pore size.

The rejection is MAINTAINED

7. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0512767 in view of US Patent 4,118,336, and US Patent 6,056,877 as applied to claims 1, 3-5, 10, 12, and 15-18 above, and in further view of WO 99/13976.

The teachings of EP 0512767 in view of the '336 patent and the '877 patent are applied as they are applied in the rejection of claims 1, 3-5, 10, 12, and 15-18 previously in this office action.

EP 0512767 in view of the '336 patent and the '877 patent does not teach the sequence of steps required in claims 19 and 20 wherein fluids are brought into contact with the solid support by inserting one opening of a unit for isolation and purification into a fluid (first sample, second washing buffer, third desorbing solution), creating a reduced pressure in a container by a differential pressure generator to suck the fluid into the chamber and into contact with the hydroxyl group, and creating an increased pressure within the chamber which results in discharge of the fluid from the chamber. Claim 19 requires the repetition of these steps for three different fluids, while claim 20 requires the repetition of these steps for only the sample and the desorbing solution.

WO 99/13976 teaches methods for isolation of nucleic acid from samples and teaches automated steps of loading a sample into a container with at least two openings (p. 7, lines 11-12), loading a wash into the container (p. 7, lines 13-17), and loading desorbing buffer (referred to as elution buffer) into the container (p. 7, lines 18-23). WO 99/13976 teaches the use of vacuum pumps for the movement of solutions into and out of the isolation chamber (p. 8, lines 6-14; 21-22). WO 99/13976 specifically teach that methods in which the sample is loaded via aspiration which occurs via the insertion of the opening of the chamber into the sample and the application of negative pressure to suck the sample into the chamber (p. 10, exemplified p. 23). Further, WO 99/13976

teaches methods in which the gases are pumped into the chamber which increases pressure in the chamber and forces fluid out of the chamber (p. 12, lines 13-15).

Thus, in view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the methods taught by EP 512767 in view the '336 patent and the '877 patent, to include the sample processing methodologies taught by WO 99/13976. One would have been motivated to apply the methods of WO 99/13976 to the methods taught by EP 0512767 in view the '336 patent and the '877 patent, in order to have provided methods for applying the fluids necessary to practice the methods taught by EP 0512767 to the solid supports for the isolation of nucleic acids.

Response to Remarks

8. Applicants have traversed the rejection, arguing that the combined references fail to teach or suggest the elements of 'selecting a rate of surface saponification and pore size of a solid phase, said solid phase being a porous film of a surface-saponified acetylcellulose'. This argument and the amendments to the claims have been fully and carefully considered but are not found to be persuasive. As noted above, the cited references teach the required limitations as recited in the claims. The claims only require selecting a rate of surface saponification and a pore size, and have no requirement that the saponification rate and pore size are selected with specific regard to the 'nucleic acid having a predetermined length' that is separated and purified. As noted in the rejection, the '336 reference does teach the step of saponification of

cellulose acetate, and the cellulose acetate is inherently porous (see also '336 reference col.8 lns.55-68). Thus in any method where cellulose acetate is used, the user is inherently selecting a rate of saponification as well as a pore size.

The rejection is MAINTAINED

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 3-5, 9, 10, 12, 13, and 15-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some amount of separation of a 1.3kb DNA fragment from a 48kb DNA fragment in a mixture containing said DNA fragments, using surface saponified triacetlycellulose, does not reasonably provide enablement for the separation of any sized nucleic acid fragments from one another from within a mixture containing any number and type of nucleic acid fragments of differing lengths using any other organic macromolecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The nature of the invention is a method for separating and purifying a nucleic acid of a predetermined length from a mixture of nucleic acids using solid phase organic macromolecule, and more specifically using a porous membrane consisting of surface

saponified triacetlycellulose. Alteration of the surface saponification rate of acetylcellulose and the size of the pores in a film made from the compound allows for the adsorbing of particularly sized nucleic acids, and their subsequent purification by desorbing. The nature of the invention requires knowledge of the relationship of the surface saponification rate of organic macromolecules and film pore size with recovery rate of any particular length of nucleic acid.

The claims encompass the separation and purification of any type of nucleic acid (e.g. DNA or RNA) from a nucleic acid mixture of any complexity (i.e. containing any amount of nucleic acids of any length). Claims 1 and 11-20 encompass the use of any organic macromolecule having hydroxyl groups. Claims 2, 3, 6, 7 and 10 encompass the use of any surface saponification rate; and claims 4 and 5 encompass the use of any surface saponification rate higher than 5% or 10%, respectively. Claim 8 encompasses the use of any surface saponification rate with any pore size; and claim 9 encompasses the use of any surface saponification rate higher than 10% and any pore size between 0.1μm and 10μm.

State of the prior art, level of skill, and level of unpredictability

While the level of skill in the art of nucleic acid separation is high, the state of the prior art with regard to nucleic acids binding to acetylcellulose indicates a high level of unpredictability. The prior art does not teach any correlation between particular saponification rates or pore sizes and the ability of an organic macromolecule to separate nucleic acids of specific lengths from mixtures of nucleic acids.

Several references teach that cellulose acetate membranes will not bind to DNA. GE Osmonic (1997) teaches the use of cellulose acetate membranes to filter nucleic acid probes, indicating the membrane is ideal because it is a non-DNA binding polymer. Similar statements about cellulose acetate are taught in two recent references: Corning (2005) indicates that cellulose acetate is inert, and does not bind either DNA or protein, and Whatman (2005) indicates that ability of DNA to bind to cellulose acetate is 'very low'.

It is also unpredictable how the sequence of any particular DNA might affect its ability to be separated in a size dependant manner using the methods described by the instant specification. Yang et al (1998) teach that DNA molecules with particular sequences (Table 1, p.5465) can bind tightly and specifically to cellulose. It would therefore be unpredictable how the presence of any of the indicated 'cellulose-binding DNA aptamer' sequences, within a larger nucleic acid sequence, would affect the separation of the nucleic acid by the method of the instant application regardless of the saponification rate or pore size of a medium containing an organic macromolecule with hydroxyl groups.

Van Oss et al (1987) indicate the unpredictability of different nucleic acids (e.g. DNA versus RNA) binding to acetylcellulose. The reference teaches that while interaction between DNA and cellulose esters can be considerable, the binding energy of RNA to cellulose esters is low (p.53). Table IV (p.60) indicates the clear difference in free energy of adhesion of DNA on cellulose acetate versus RNA on cellulose acetate; the reference teaches that DNA should bind more strongly to cellulose esters that RNA

(p.61), and RNA is much more weakly attracted to cellulose esters than DNA (p.63). Pan et al (2003) teaches the inherently different structural properties of DNA versus RNA. The reference indicates that different chemistries of DNA and RNA allow for different flexibilities and the adoption of different conformations, thus making it unpredictable as to how these different molecules would interact with the membranes (i.e. varying saponification rates and pore sizes) discussed in the instant application.

Direction provided and presence of working example

The instant specification asserts that nucleic acids can be separated and purified by preparing a plurality of porous membranes with varying surface saponification rates and varying pore sizes. The specification provides data regarding the recovery rate of two DNA fragments (1.3kb and 48kb) from various preparations of triacetylcellulose (p.28, Tables 3 and 4; Fig 5). The specification teaches that recovery rate (that is the percentage of the DNA that is applied to a membrane which is adsorbed to the membrane and then desorbed from the membrane) varies between two different saponification rates (either 50% or 100%) and four different pore sizes (0.2, 0.4, 1.0, or 2.5μm). There is no other information provided for any other saponification rates or pore sizes. Notably, there is no information contained within the specification for saponification rates lower than 50% (as are encompassed by the claims, for instance claims 4 and 5 which particularly point out saponification rates with lower limits of 5% and 10%, respectively). Similarly, there is no other information provided for any pore size other than those listed in Table 1; notably there is no information in the

specification concerning pore sizes larger than 2.5μm (as are encompassed by the claims, for instance claim 9 which particularly points out pores sizes as large as 10μm).

The specification indicates (pp.10-11) the following saponification rates combined with the following pore sizes will allow the recovery (by adsorbing and subsequently desorbing) of particularly sized DNA: both low molecular weight DNA and high molecular weight DNA were recovered from 100% saponified membranes with 0.2μm pores; recovery of high molecular weight DNA is relatively higher (compared to recovery of low molecular weight DNA) from 50% saponified membranes with 0.2μm pores; the recovery rate of high molecular weight DNA is high from 100% saponified membranes with 2.5μm pores.

The specification provides a single example of the purification of a low molecular weight nucleic acid and a high molecular weight nucleic acid from a nucleic acid mixture (pp.28-29). This example demonstrates the separation of a 1.3kb fragment from a 48kb fragment which had been mixed together in an aqueous solution. In the example, the different DNAs are separated by the sequential action of a first membrane (100% saponified, 0.2 μm pore size) and a second membrane (50% saponified, 0.2 μm pore size). And while the specification asserts that it is clear from the results of Fig. 5 (a photograph of an agarose gel) that a nucleic acid having a desired size can be purified by selecting saponification rate and pore size, there is no quantification of the results to indicate the resulting level of separation. For instance, regarding the isolation of the 1.3kb DNA (condition (c) on p.29) from a mixture containing 10μg each of a 1.3kb DNA and a 48kb DNA (as in (4) on p.27), one would expect (based on the collection rate

information presented in Tables 3 and 4) for the final recovered product to contain 7.7µg of 1.3kb DNA and 1.4µg of 48kb DNA.

The specification does not provide any example of the separation of any other nucleic acid mixtures other that the 1.3kb and 48kb mixture described in Example 1, or results concerning recovery rates from any other saponification rates or pore sizes than those presented in Tables 3 and 4. It is unknown what resolution of separation would be attainable with other membrane and/or nucleic acid mixture conditions. For instance, are there any possible conditions that would allow for the separation of a 9kb DNA fragment from an 11kb DNA fragment. Additionally, while the specification refers to conditions for purification of high molecular weight versus low molecular weight molecules, the specification refers to a 10kb fragment as both a relatively long nucleic acid (p.12 ln.1) and a relatively short nucleic acid (p.12 ln.11).

The specification does not provide any guidance concerning the separation of any nucleic acid mixtures containing anything other than the double stranded DNA of Example 1.

Quantity of experimentation required

A prohibitive amount of experimentation would be required to use the claimed invention in its full scope. For any given mixture of nucleic acids, one would have to establish the recovery rate of a nucleic acid of interest having a particular length under different saponification and pore size conditions. One would also have to determine if the described methods would be compatible RNA, or perhaps with other types of nucleic acids such as peptide nucleic acids (PNA).

Alteration of saponification rate alone would require a large quantity of experimentation. The specification indicates conditions used to achieve either 50% or 100% saponification (p.26), however there is no way to predict what conditions are needed to achieve any other saponification rates (e.g. what concentration of sodium hydroxide solution to use, and how long to treat a membrane). The specification only indicates that altering sodium hydroxide concentration can change saponification rate (p.10), and that the rate is determined by quantifying remaining acetyl groups by NMR.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and scope of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of a working examples, it is the conclusion the an undue amount of experimentation would be required to use the invention in the full scope of the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st paragraph. Applicants arguments and amendments to the claims have been fully and carefully considered but are not found to be persuasive.

Applicants argue (p.14 of remarks) that the present claims are drawn to methods using acetylcellulose, and not drawn to the use of 'any organic macromolecule'. The examiner maintains that the specification of the instant application provides examples only of the use of triacetylcellulose, whereas the claims encompass the use of any

acetylcellulose (e.g. diacetylcellulose) for which no experimentation concerning the use of specific saponification rates and pore sizes of films in regard to separation of nucleic acids of particular predetermined lengths have been performed.

Applicants further argue that the specification is enabled for the purification of any sized nucleic acid. Applicants remark that the specification teaches a skilled artisan guidance to separate a wide size range of nucleic acid fragments, and points to (page 14 of remarks) Example 1 of the specification which:

> 'describes the separation of a 1.3 kb nucleic acid fragment or a 48 kb fragment from a nucleic acid mixture. Thus, the specification teaches a skilled artisan how to separate both low molecular fragments and high molecular weight fragments'.

Applicant further argues that the provided Declaration 'demonstrates separation of a 200 bp fragment and a 1,500 bp fragment', claiming there is thus evidence for separations 'over three orders of magnitude of size range'. These arguments are not considered persuasive. The examiner maintains that the claims require the separation and purification of a nucleic acid of a predetermined length from a sample solution 'wherein the solution contains nucleic acids of different lengths', and the claims thus encompass the separation of any sized nucleic acid from a solution containing any sized nucleic acids. Applicants Examples (from the filed specification and the Declaration) demonstrate only the separation of nucleic acids in a mixture containing short nucleic acids (200 bp, or 1,300 bp, or 1,500 bp) from very long nucleic acids (48,000 bp). Thus Applicants characterization of the examples as teaching 'how to separate both low molecular fragments and high molecular weight fragments' and

providing evidence for separations 'over three orders of magnitude of size range' does not serve to address the requirements of the claimed method.

Thus, the Declaration under 37 CFR 1.132 filed 05/22/2006 is insufficient to overcome the rejection of claims 1, 3-5, 9, 10, 12, 13, and 15-22 based upon 35 usc 112 first paragraph (scope of enablement) as set forth in the last Office action because: The showing of the declaration is not commensurate in scope with the breadth of the claims.

As addressed in the rejection, the provided examples do not serve to enable one skilled in the art to separate nucleic acid of a predetermined length from a mixture or nucleic acids of similar lengths.

Applicants further assert that the specification describes how to separate and purify nucleic acids of predetermined lengths from a nucleic acid mixture that contains nucleic acid fragments of different lengths (remarks p.14, last paragraph). As discussed above, the examiner maintains that the provided examples do not serve to enable one skilled in the art to separate nucleic acid of a predetermined length from a mixture or nucleic acids of similar lengths. And while Applicants point to page 12 lines 4-14 of the specification and assert that the specification teaches a general method for separating a nucleic acid of a particular length from 'any particular mixture that contains nucleic acid fragments of different lengths', the examine maintains that the specification (page 11 ln.35 – page 12 ln.14) asserts that markedly different conditions (i.e. different saponification rates) are suitable for the purification of a nucleic acid of 10kb (where the specification teaches that a 10kb nucleic acid is considered both a long nucleic acid and

a short nucleic acid). Thus the specification does not in fact teach the skilled artisan how one may a priori identify a triacetylcellulose membrane suitable for the purification and separation of a nucleic acid of a particular length. Thus the required experimentation alluded to by the specification (i.e. measuring the recovery rate of each nucleic acid using membranes having various saponification rates and various pore sizes, page 11 lns.26-34) would require the testing of various conditions to determine saponification rate and pore sizes required to separate any nucleic acid of a particular length for any nucleic acid mixture. The specification does not establish that such conditions exists which would allow for the separation of similarly sized nucleic acids from a mixture, for example the separation of a 9,900 bp nucleic acid from a 1,100 bp nucleic acid.

Applicants further argue that the references cited by the examiner that state cellulose acetate membranes will not bind DNA, that certain DNA molecules bind tightly to cellulose, and that the binding energy of RNA to cellulose esters can be low are not persuasive because the references do not discuss the level of predictability of the ability of nucleic acids to bind to surface saponified acetylcellulose. The examiner maintains that these references, in light of the lack of any teaching in the prior art as to how one might a priori identify a saponification rate of pore size of an acetylcellulose membrane suitable for the separation of any nucleic acid of a particular length from a mixture of nucleic acids, demonstrate the unpredictability in using any cellulose acetate to purify any nucleic acid.

The rejection is MAINTAINED

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1, 3-5, 9, 10, 12, 13, and 15-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-7, and 9-20 of copending Application No. 10/621,329. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '329 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified

acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium. Additionally, the claims of the conflicting application require selection of a saponification rate and, because acetylcellulose is inherently porous, selection of a pore size.

Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1, 3-5, 9, 10, 12, 13, and 15-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 6, and 8-18 of copending Application No. 10/621,412. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '412 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium.

Additionally, the claims of the conflicting application require selection of a saponification rate and, because acetylcellulose is inherently porous, selection of a pore size.

Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 1, 3-5, 9, 10, 12, 13, and 15-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 6, and 8-18 of copending Application No. 10/209,336. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '336 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium.

Additionally, the claims of the conflicting application require selection of a saponification rate and, because acetylcellulose is inherently porous, selection of a pore size.

Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1-7 and 10-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-26 of copending Application No. 10/975,469. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '469 application recite a method comprising the same steps as the method of the instant application: absorbing and desorbing nucleic acid to and from a solid phase material containing hydroxyl groups, specifically surface saponified acetylcellulose, the use of solubilization reagents, washing and desorbing buffers, and particular separation units and steps for contacting nucleic acids with a purification medium.

Additionally, the claims of the conflicting application require selection of a saponification rate and, because acetylcellulose is inherently porous, selection of a pore size.

Because the methods of the copending claims recite the relevant features of the rejected claims, they would inherently be capable of accomplishing the intended use of the rejected claims as detailed in the rejected claims, specifically separating and purifying a nucleic acid having a predetermined length.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

Applicant has not traversed the double patent rejections set forth in the Office Action; the rejections as set forth are MAINTAINED.

Conclusion

No claim is allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER